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Metastatic Nonfunctional Retroperitoneal Paraganglioma

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Derek Jenkin, MD (Pediatric Radiation Oncologist)

I would like to welcome everyone to tumour board. Today we shall discuss the case of a patient whom we still see regularly, and who was diagnosed with a non-functioning paraganglioma over 10 years ago. Dr. Chow will start with the history.

Edward Chow, MD (Radiation Oncology Resident)

In April 1986, G.B. a 14-year-old male, was admitted to a community hosppital with a 2 day history of right upper quadrant abdominal pain. Physical examination revealed a right upper quadrant abdominal mass and an abdominal ultrasound confirmed this finding. The patient was transferred to the Hospital for Sick Children where further imaging was obtained and a core biopsy was performed. Dr. Babyn, could you review the staging investigations for us?

Paul Babyn, MD (Pediatric Radiologist)

Unfortunately, the patient had a history of contrast allergy and so all the CT scans were done without contrast. The abdominal CT performed here showed a right-sided retroperitoneal mass 11.8 cm × 9.2 cm in diameter extending 15 cm in length from the porta hepatis superiorly to the inferior mesocolon (Figure 1). There was no evidence of biliary or renal obstruction. The inferior vena cava was not well opacified, but was expanded and IVC invasion could not be excluded. An IVP revealed only displacement of the right ureter, with normal kidneys. The CT scan of the chest and the bone scan were normal.

Dr. Chow. The core biopsy was reported as showing nests of tumour cells with pale eosinophilic cytoplasm arranged in aggregates within a fibrovascular stoma. These features led to the diagnosis of paraganglioma. Urinary VMA and HVA were normal. The patient had no abnormal cardiovascular signs or symptoms, so the working diagnosis was non-functioning paraganglioma. Dr. Banerjee, it is apparently quite uncommon for the diagnosis of paraganglioma to be made on preoperative biopsy. Why is that?

Diponkar Banerjee, MD (Pathologist)

The most characteristic findings are seen with surgical specimens and include polygonal or slightly spindled cells with pale eosinophilic cytoplasm forming clusters or anastomosing sheets separated by thin walled blood vessels—the so called ''Zelballen.'' The diagnosis can be made with fine needle cytology preparations, however, which show characteristic chief cells with pleomorphic nulcei, prominent nucleoli and usually finely granular eosinophilic cytoplasm [1]. This case was unusual in that the diagnosis was made with a core biopsy that was sufficiently large to identify ''Zelballen.''

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Fig. 1. Staging CT scan from April 1986 demonstrating a large retroperitoneal mass at diagnosis.

Dr. Jenkin. Dr. Shandling, could you tell us about the operation that was undertaken?

Barry Shandling, MD (Pediatric Surgeon)

Yes, I remember it quite vividly. In May of 1986, we attempted to resect the tumour. It looked well encapsulated and extended from the inferior surface of the liver to the colon. You can see from my O.R. note that it involved the duodenum, the pancreas, and the inferior vena cava. It was extremely vascular and even with gentle blunt dissection, the tumour bled profusely. The patient required twenty-one units of packed red cells and the resection had to be abandoned before completion. After the patient recovered, we sent him for tumour embolization with the hope that it would make resection easier.

Tara Williams, MD (Pediatric Radiology Fellow)

Angiography demonstrated that the major feeding vessels were lumbar arteries from L1 to L3 and vessels arising from the abdominal aorta. Embolization of the tumour was performed twice. Post-embolization angiography revealed good occlusion of major feeders, with some residual supply from the right renal and inferior mesenteric arteries. Although the IVC was patent, there were two areas where tumour appeared to be within the lumen.

Dr. Shandling. In June, 1986 we were able to perform a gross total resection of the tumour that included taking a portion of the IVC. Even after embolization, the patient required 10 units of packed red cells, although he recovered quickly from surgery without any postoperative complications.

David Hodgson, MD (Radiation Oncology Resident)

Most case series report that non-functioning paragangliomas are highly vascular, although unlike in this case, the histologic diagnosis is usually made after surgery. Did you find that the embolization made the surgery easier and would you use it again in the future if you had a preoperative diagnosis?

Dr. Shandling. Absolutely. The tumour was much softer and less vascular after the embolization. Particularly if I were dealing with a large tumour like this one, I would have it embolized before attempting resection.

Dr. Hodgson. The specimen submitted showed the tumour to be 14 cm × 9 cm × 6 cm. The pathology was reviewed by Dr. Banerjee.

Dr. Banerjee. There was marked necrosis although approximately 50% of the tumour appeared viable. The characteristic pale eosinophilic cells forming Zelballen confirm the diagnosis of paraganglioma (Figure 2). The tumour sections revealed vascular invasion, consistent with the preoperative imaging and the operative findings.

Dr. Hodgson. Are there any histologic features that can be used to predict the malignant potential of these tumours?

Dr. Banerjee. Histologic criteria for malignancy are controversial. While many authors assert that the malignant potential of these tumours can only be gauged by the

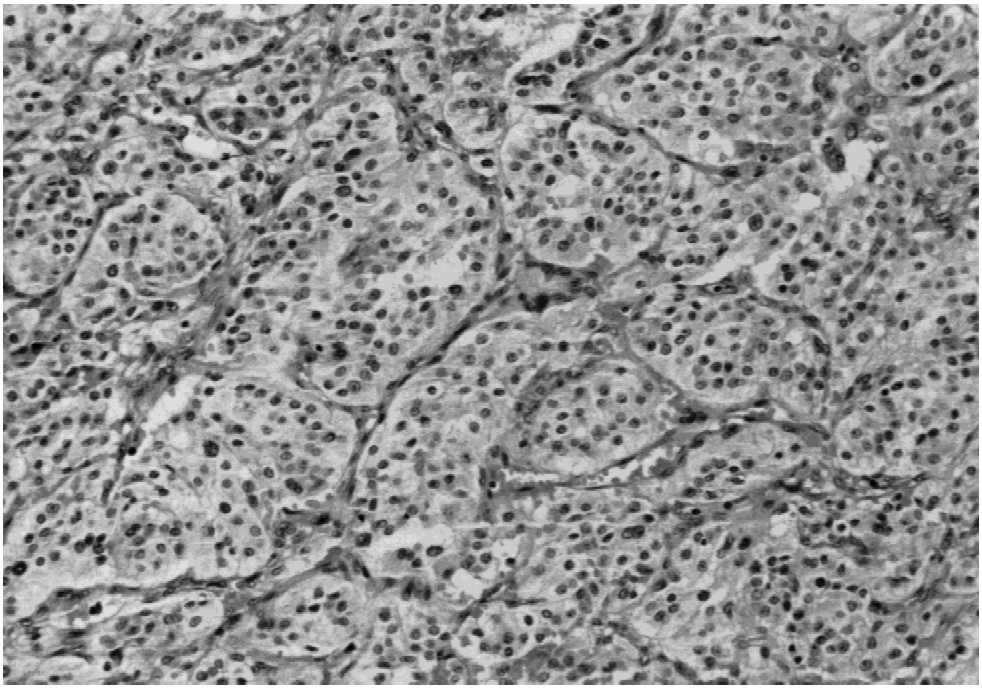

Fig. 2. Section from surgical specimen stained with hematoxylin and eosin, showing nests of cells in a vascular stroma.

clinical course, Linnoila et al. have suggested that extra-adrenal location, coarse nodularity, confluent necrosis and the absence of hyalin globules may be predictive of malignancy [2]. This patient's tumour demonstrated all of these features, as well as vascular invasion. Some authors have suggested that non-diploid tumours are likely to be malignant, but others have found no difference in ploidy or DNA content variability between clinically benign and malignant neoplasms [3,4].

Dr. Hodgson. The patient was well and active following surgery, but in November 1986, follow-up ultrasonography showed that the inferior vena cava was distended by a 5.4 cm × 3.5 cm × 3.5 cm mass located just above the renal hilum. It was unclear whether this represented tumour or thrombus. A repeat ultrasound study in February, of 1987 showed the mass to be 6.2 cm × 4.3 cm and a subsequent MRI of the area was reported as demonstrating recurrent tumour in the IVC. The patient was completely asymptomatic. No intervention was undertaken. By March 1989 an ultrasound examination revealed that the IVC mass had grown to 9 cm × 7 cm × 6 cm. The patient remained well. A CT of the abdomen and pelvis was performed.

Dr. Williams. In May 1989, the CT and abdomen of the pelvis showed that the abdominal mass measured approximately 8 cm × 6.5 cm, with no other intra-abdominal masses visible. There were, however, new lucent defects in vertebral bodies T12, L1, L2, and the sacrum, consistent with bony metastases. A bone scan in June of 1989 showed increased uptake in the left scapula and spine. Plain X-ray films of the left shoulder revealed a lytic lesion within the acromion and scapular spine.

Dr. Hodgson. An orthopedic consultation was obtained and a biopsy of the scapula confirmed metastatic paraganglioma. Remarkably, the patient remained asymptomatic.

Dr. Chow. Could radiodinated meta-iodobenzyl guanidine (MIBG) be used to localize metastases from nonfunctioning paragangliomas?

Dr. Williams. Yes, a paraganglioma can take up MIBG irrespective of whether it is functional or not. I-123 labelled MIBG can localize approximately 50% of nonfunctioning tumours [5].

Dr. Jenkin. In this perfectly well 17-year old, the disease, unequivocally, had spread to new sites. This might have been the time to intervene. Dr. Greenberg, can you tell us what role chemotherapy might have in this situation?

Mark Greenberg, MB (Pediatric Oncologist)

As you would expect with a disease like paraganglioma, the retrospective series have small numbers of patients and often include different histologies, and patients who have already received some form of treatment. In a group of 13 patients with metastatic carcinoid or paraganglioma given carboplatin-based chemotherapy, symptomatic response occurred in 8 patients although no objective tumour responses were reported [6]. Other chemotherapy agents investigated included doxorubicin, doxorubicin plus fluorouracil (5-FU), cisplatinum, and

Fig. 3. Unenhanced CT of May 1996 showing ill-defined soft tissue mass in the porta hepatis, contiguous with the inferior vena cava, aorta, and portal blood vessels. Also seen is a lucent vertebral metastatic lesion in L2 (↑).

streptozotocin plus 5-FU, with response rates for these agents ranging from 7% to 26% [7,8]. Since chemotherapy would not have been curative and since the patient was feeling perfectly well, we decided not to treat him at that time.

Dr. Chow. Is there any role for therapeutic doses of MIBG in this scenario?

Dr. Greenberg. Again, the data come from very small series or case reports, but it does appear that MIBG can provide complete or partial symptom relief in some patients, and occasional partial tumour regression. Even when the different reports are taken together, though, the numbers are so small it's difficult to make any meaningful estimation of the probability of response. Many reports reflect a mixed patient population with paraganglioma as one among other neural crest tumours. The benefit of MIBG treatment is that there is virtually no toxicity. Even so, in an asymptomatic patient, I would not intervene [9,10].

Dr. Jenkin. Dr. Danjoux, could you tell us about the response of paraganglioma to radiation treatment?

Cyril Danjoux, MD (Pediatric Radiation Oncologist)

Radiation treatment can provide substantial pain relief in most patients with bony metastases, and may cure some so-called glomus tumours of the head and neck; that is, jugulotympanic paragangliomas. Symptom relief may be slow, however, and persistence of radiologic and clinical masses is common [11–14]. These clinical observations account for the earlier opinion that radiation treatment has no significant effect on these tumours. With the slow pace of disease seen in many cases, conservative symptomatic management alone is appropriate for grossly resected or early metastatic disease, reserving treatment for symptomatic progression.

Dr. Hodgson. In view of this patient's vertebral metastases, what would be the role of irradiation if he developed a spinal cord compression?

Dr. Danjoux. Symptomatic relief of cord compression following radiation treatment alone has been reported with improvement of CSF block and neurologic symptoms on follow-up myelogram. More commonly, radiation treatment is used as adjunctive therapy after surgical decompression of the spinal cord [15,16].

Dr. Jenkin. This case demonstrates that metastatic paraganglioma may have a very long natural history without treatment. We should be cautious about attributing prolonged survival to any given treatment modality, particularly in the setting of metastatic disease. We continue to follow this patient with annual CT scans of his abdomen and pelvis. His most recent CT in May 1996 revealed that the retroperitoneal mass measured 6 cm in AP diameter, and that lytic lesions in T12 to L2 and in the right sacrum had not changed since 1989 (Figure 3). The patient remains well and symptom-free, is now 25 years old and has lived with untreated metastases for over 10 years. It seems likely that he will require palliative treatment of some sort in the future, but if his history to

date is any guide, it may be a number of years before this is required. Dr. Hodgson, what did you find in your review of the literature?

Dr. Hodgson. A series of 22 patients with retroperitoneal paragangliomas was reported by Sclafani et al. [17]. The median age of the patients was 42, with an equal distribution of males and females. The youngest patient was 11, although these neoplasms have been reported in patients as young as age 5 [18]. Sixty-four percent of these tumours were non-functioning. Among 13 patients who underwent apparently complete resection, 2 subsequently developed local relapse, while 5 had distant failure. Overall, 50% demonstrated malignant clinical behavior [17].

Metastases commonly occur in the bones of the axial skeleton, but may also arise in the liver, biliary tract, ovary, lungs, or lymph nodes. Sclafani et al. report median survival after the development of metastatic disease was 34 months, with the longest survivor living 76 months [17]. There is a report from Finland of a patient with lung metastases who survived 9 years without treatment [19]. A series from the M.D. Anderson Hospital includes a patient with paraganglioma metastatic to bone and lymph nodes who was alive after 300 months, and another alive after 100 months of follow-up, although both received chemotherapy [20]. The patient presented here represents an extreme example of the slow progression characteristic of paraganglioma.

Surgical resection is the mainstay of treatment for patients with non-metastatic paraganglioma. These tumours are highly vascular and frequently involve the aorta or IVC, which can complicate resection. As in this case, arterial embolization has been successfully used to facilitate excision, particularly for tumours arising in the neck that involve critical vascular or neurologic structures [21].

Cummings et al. used radiotherapy alone to treat symptomatic glomus tumours of the head and neck, resulting in complete relief of 48% of symptoms and durable local control in 42 of 45 (93%) patients, although good clinical outcome was not always associated with significant tumour shrinkage [13]. Radiotherapy can provide effective pain relief for patients with bony metastases and has been used adjuvantly following surgery for spinal cord compression, although its added benefit as an adjuvant treatment will likely never be proven due to the rarity of these tumours [17].

As Dr. Greenberg discussed, chemotherapy can produce tumour regression in a few patients with metastatic disease, with resulting symptomatic relief. As has also already been mentioned, MIBG has been used extensively in the imaging and treatment of malignant pheochromocytomas. It is an analogue of noradrenalin that is taken up by a number of different neuroendocrine tumours. MIBG uptake does not correlate well with the functional status of paragangliomas, though it has been associated with the number of neurosecretory granules seen in tumour sections [22]. In a series of 15 patients, MIBG was able to identify 13 of 24 (54%) functioning or nonfunctioning paragangliomas [1]. Although its effectiveness is not well documented, case reports demonstrate that nonfunctioning paragangliomas may respond to MIBG therapy [23].

There have been multiple reports of patients with metastatic paraganglioma treated with combinations of surgery, chemotherapy, and radiotherapy who have gone on to enjoy prolonged survival, a result often attributed to the treatment. This case, and others reported, show that patients with metastatic disease may survive for prolonged periods without treatment [19]. Therapy is clearly indicated to palliate symptomatic metastases, but should not be provided with the intent of prolonging survival. There is no good evidence that any intervention reliably achieves that goal. The patient remained asymptomatic when seen in October, 1997.

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SERIES CO-EDITOR'S NOTE

Glomus (Latin: ball) describes the rounded neurovascular structures found in various anatomic sites; e.g., the para-aortic regions and the tip of the coccyx along with the more familiar loci at the bifurcation of the carotid artery and the bulb of the jugular vein. These last two are known as the *glomus carotideum* and the *glomus jugular*, respectively, and are the most common of the sites where glomus tumors develop. The *glomerulus* (little ball) is an apt word for that kidney structure. From the same word stem *glomerate* and *agglomerate*, with the sense of rolling or gathering things into a ball.

The very similar Latin word *globus* (a ball) gives rise to unexpected secondary meanings. These have to do with the subjective sensation of there being a ball or lump present somewhere in the body. *Globus hystericus*, for instance, specifically indicates such a disconcerting sensation in the throat.

Carotid has an even less obvious derivation from the Greek *karos* = deep sleep, but is logical nonetheless. It was known to the ancients and to the *hashashashin* (Arab = hashish eaters) (assassins) that pressure on the two *g. carotideum* would rapidly stupefy a person, and render him defenseless. The *hashashashin*, who have been discussed in these pages before,* were a secret Persian sect of the 11th century organized to eliminate leaders of the Christian community.

Embolization comes from the Greek *embolos* = plug and *ballein* = to throw; hence, ''to throw a plug.'' Ballein has rich and varied offspring. From *paraballein* (to throw beside; to compare) come a host of words useful both literally and figuratively: *parabola* in mathematics, *parables* in literature and oratory; and via the Latin *parabolare* (to speak in parables) to *parler* (French = to speak) whence *Parliament* and even *parlor*, which in ancient spelling and usage indicated ''the room where speaking takes place.''

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